

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: EDWARD D. GRIEFF
HALE AND DORR LLP
1455 PENNSYLVANIA AVENUE, NW
WASHINGTON DC 20004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 102258.350	Date of Mailing (day/month/year) 11 JUL 2000
International application No. PCT/US00/05286	International filing date (day/month/year) 01 MARCH 2000
Applicant NITROMED, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT GERSTL Telephone No. (703) 308-1235
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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 102258.350	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US00/05286	International filing date (day/month/year) 01 MARCH 2000	(Earliest) Priority Date (day/month/year) 01 MARCH 1999
Applicant NITROMED, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/05286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 405/00; A61K 31/557

US CL : 560/121; 562/503; 514/530, 573

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 560/121; 562/503

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,922,293 A (MOROZOWICH) 25 November 1975, Ex. 3.	2
X	WO 98/58910 A2 (NICOX, S.A.) 30 December 1998, Ex. 1.	2

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 JUNE 2000

Date of mailing of the international search report

11 JUL 2000

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ROBERT GERSTL

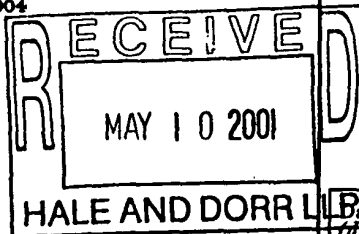
Telephone No. (703) 308-1235

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: EDWARD D. GRIEFF
HALE AND DORR LLP
1455 PENNSYLVANIA AVENUE, NW
WASHINGTON DC 20004



NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

08 MAY 2001

Applicant's or agent's file reference 102258.350		IMPORTANT NOTIFICATION	
International application No. PCT/US00/05286	International filing date (day/month/year) 01 MARCH 2000	Priority Date (day/month/year) 01 MARCH 1999	
Applicant NITROMED, INC.			

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/MB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the POT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box POT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT GERSTL Telephone No. (703) 308-1235
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Arti l 36 and Rul 70)

Applicant's or agent's file reference 102258.550	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/05286	International filing date (day/month/year) 01 MARCH 2000	Priority date (day/month/year) 01 MARCH 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 405/00; A61K 31/557 and US Cl.: 560/121; 562/503; 514/530, 573		
Applicant NITROMED, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

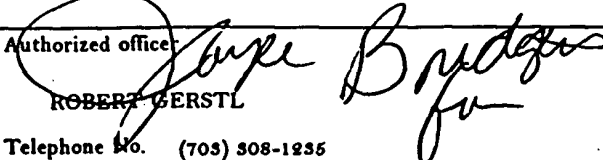
2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 12 SEPTEMBER 2000	Date of completion of this report 19 APRIL 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box P0T Washington, D.C. 20231	Authorized officer  ROBERT GERSTL
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/05286

I. Basis of the report**1. With regard to the elements of the international application:***☐ the international application as originally filed☒ the description:

pages (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages (See Attached) _____, as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages (See Attached) _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages _____ NONE☒ the claims, Nos. _____ NONE☒ the drawings, sheets/fig. _____ NONE**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/05286

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims <u>1-115</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-115</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-115</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-115 the criteria set out in PCT Article 35(2)-(4), because the prior art does not teach or fairly suggest the compounds and their properties.

_____ NEW CITATIONS _____

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/05286

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Boxes I - VIII

Sheet 10

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-62, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 64-77, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Page 63, filed with the letter of 13 February 2001.

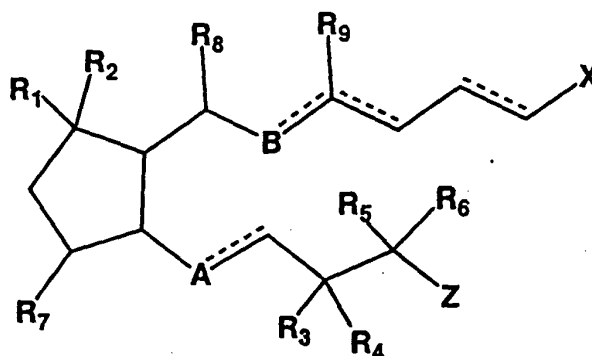
This report has been drawn on the basis of the drawings,
page(s) 1-4, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

CLAIMS

What is claimed is:

1. A prostaglandin comprising at least one NO group or a pharmaceutically acceptable salt thereof.
- 5 2. A compound of formula (I) or a pharmaceutically acceptable salt thereof wherein the compound of formula (I) is:



(I)

wherein the dotted lines indicate a single or a double bond;

R_1 is $-\text{OD}_1$ or $-\text{Cl}$;

R_2 and R_8 are a hydrogen ; or R_1 and R_2 taken together are $=\text{CH}_2$ or $=\text{O}$;

R_3 and R_4 are each independently a hydrogen, $-\text{OD}_1$ or $-\text{CH}_3$;

R_5 and R_6 are each independently a hydrogen, $-\text{OD}_1$, $-\text{CH}_3$, $-\text{OCH}_3$ or $-\text{CH}=\text{CH}_2$;

R_7 is a hydrogen or $-\text{OD}_1$;

R_9 is hydrogen or absent when the carbon to which it is attached is the central carbon of an allene functionality; or R_8 and R_9 taken together with the chain to which they are attached form a substituted benzene ring with the proviso that R_1 is an oxygen atom which is attached to the carbon atom at the position of the benzene ring defined by B;

A is $-\text{CH}=\text{}$, $-\text{CH}_2$, $-\text{S}$, or $-\text{O}$;

B is $-\text{CH}=\text{}$, $-\text{CH}_2$, $-\text{S}$, or $-\text{C}(\text{O})$;

X is $-\text{CH}_2\text{OR}_{11}$, $-\text{C}(\text{O})\text{OR}_{11}$ or $-\text{C}(\text{O})\text{N}(\text{D}_1)\text{R}_{12}$;